The Effect of Physical Training Upon the Mechanical and Metabolic Performance of the Rat Heart

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ABSTRACT The dynamic and metabolic performance of rats conditioned by a swimming program (CH) and hearts of sedentary rats (SH) was studied in an isolated working rat heart apparatus. Heart rate, filling pressure, and afterload were controlled or kept constant, and heart weights were comparable in both groups.

When compared with SH, CH had increased cardiac output and cardiac work. Atrial pacing at more rapid rates caused greater differences in these functions, and left ventricular pressure and maximal rate of pressure rise (dp/dt) became higher in CH than in SH. Atrial pacing was associated in CH with increased oxygen consumption but in SH by increased lactate and pyruvate production.

When atrial filling pressure was elevated in order to perform ventricular function curves, CH showed greater dynamic responses than SH. There were also greater increments in oxygen consumption, and the ratio of aerobic to anaerobic energy production was also higher in CH.

The mechanism of increasing oxygen consumption during stress in CH was mainly by improved coronary flow. In SH coronary flow did not change, but extraction of oxygen from the perfusing fluid increased.

The results indicate that in physically trained rats the function of the heart as a pump is improved. These hearts have greater aerobic and mechanical reserve than hearts of sedentary animals. These effects appear to be at least partially due to improved mechanisms of oxygen delivery.

INTRODUCTION

Epidemiological studies indicate that physical conditioning may be protective against disease of the cardiovascular system (1). Studies of deconditioning and conditioning demonstrate that cardiac performance is altered by the presence or absence of regular physical exercise (2). Most studies of the effects of physical training on the heart have concerned themselves with cardiac performance in the intact animal or human. Such studies do not furnish knowledge of intrinsic cardiac performance, not influenced by neurohumoral or other compensatory mechanisms. Direct experiments in the open chest rat (3) or using isolated trabeculae carneae (4) indicate that myocardial tension development is elevated in hearts of conditioned animals.

The effects of physical training upon cardiac metabolism have not been extensively studied. Elevations in cardiac glycogen (5–7), minor changes in cardiac triglyceride levels, and normal levels of high energy phosphate compounds have been reported (7). Lactic dehydrogenase activity has also been found to be increased (8). Myocardial catecholamine levels are diminished in hearts of conditioned rats (9).

The purpose of the present investigation was to study the dynamic and metabolic performance of hearts from conditioned rats in a system that was free of the neurohumoral and peripheral vascular compensatory influences. Metabolic and dynamic measurements were made in isolated working rat hearts during the steady state at intrinsic heart rates and with pacing. The responses to increasing the left atrial pressure were also investigated. The results indicate that when hearts from conditioned animals are perfused under isolated conditions they exhibit increased metabolic and dynamic performance in the steady state. When stress is imposed, hearts from conditioned animals have greater maximal aerobic and dynamic capacities.

METHODS

The conditioning program. Male Sprague Dawley rats, with an original weight of 180–200 g, were swum 75 min twice daily for 5 days/wk. A deep tank of water kept at a temperature near 33°C was used for swimming. The diameter of the tank was 17.5 inches, and five to seven rats were swum at once. This geometry insured enough interaction between rats so that they could not passively float. The program was continued for at least 8 wk before the

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hearts were studied. A series of rats taken from the same initial group as the swimmers, but kept at normal cage activity, were used for matched sedentary controls.

Perfusion apparatus and solutions. The perfusion system is a recirculating, isolated, working rat heart apparatus of the type described and diagrammed by Neely, Liebermeister, Battersby, and Morgan (10). In this apparatus the heart is perfused through the left atrium, and it ejects fluid from the left ventricle into the aorta.

The height of the aortic column, which determines the ventricular systolic pressure, was maintained at 85 cm above the heart. The atrial filling pressure for steady-state experiments was kept at 10 cm and was varied between 5 and 20 cm when ventricular function curves were studied. The overflow of the aorta dripped into a calibrated aortic chamber that was used to measure aortic flow. The effluent fluid that dripped out of the right ventricle was the coronary flow, and this was also measured in a calibrated chamber. The volume of perfusate in the antegrade system was 200 ml. The perfusion medium was a modified Krebs-Henseleit solution (11) which contained 143 mM sodium, 123 mM chloride, 25 mM bicarbonate, 6 mM potassium, 1.2 mM magnesium, 1.2 mM phosphate, 2.0 mM calcium, 0.5 mM disodium EDTA, and 5 mM glucose. The perfusion medium used for retrograde perfusion during the time the heart was being mounted on the apparatus contained 4 U/ml heparin. The solutions were bubbled with 5% CO_2-95% O_2 gas, and in the antegrade perfusion cycle gas was also mixed into the solution by the lifting perfusion pump as diagrammed previously (12). This maintained the oxygen tension of the perfusate above 600 mm Hg and the pH close to 7.4. The whole apparatus including the tubing was water-jacketed so that perfusion was at 37°C. A 17 cm catheter led from the left ventricle to a Statham P23Gb strain gauge, which was attached to a photographic recorder (Electronics for Medicine, Inc., White Plains, N. Y).

Systolic pressures were monitored on a full scale of 0–200 mm Hg. The rate of left ventricular pressure rise (LV dp/dt) was recorded with an RC differentiating channel. The left ventricular pressure recording system, including the fluid filled catheter, had a frequency response of 21 cps. Although this frequency response might be borderline for hearts beating at a rate of 300 beats per min, any damping of the pressure curve would tend to underestimate differences in dp/dt. The time constant for the differentiating circuit was 0.5 msec, and the response was linear within 5% from 1 to 57 cps. Recordings were made at paper speeds of 100 or 200 mm/sec.

In addition to the left ventricular catheter, catheters led from the atrial perfusion chamber and the right ventricle to a Radiometer ultramicro oxygen electrode. This was connected to a Radiometer gas monitor and pH meter model 27, and it was used for determining oxygen tension (Po_2) in the "arterial" and myocardial effluent perfusion medium. A pacing wire impinging upon the right atrium was attached to a Grass SD5 stimulator. The square wave stimulus used was 1.2–1.6 v with a duration of 4 msec.

Experimental procedure. Animals were fasted and rested the day before their hearts were removed for perfusion. Whenever possible hearts from sedentary rats (SH) and from conditioned rats (CH) were paired and perfused alternately on the same day. The rats were anesthetized lightly with ether, the chest was opened, and the heart was removed quickly and placed in a beaker filled with perfusion medium at 3°C. The heart was perfused retrograde through the aorta, while the catheters were placed and the left atrium was cannulated. For catheterization of the left ventricle a polyethylene-90 catheter was constructed with a small flange on one end and with the other end beveled to a sharp point. The pointed end was inserted through a pulmonary vein into the left atrium, passed through the mitral valve, and then pierced through the free wall of the left ventricle. The flanged end then was pulled into the left ventricle and abutted against the free wall. The beveled end was connected to the Statham strain gauge. Another catheter was inserted through the pulmonary artery into the right ventricle and connected to the oxygen electrode.

Placement of all cannulas and catheters took 2–3 min. After a total of 5 min of retrograde perfusion, antegrade perfusion was begun. Periodic measurements were recorded of dynamics, Po_2 of the influent and effluent perfusion medium, coronary flow and aortic flow. In some steady-state experiments periodic samples were taken from the reservoir for measurements of lactate and pyruvate accumulation and glucose disappearance. During some ventricular function curves samples were taken from influent and effluent lines so that lactate balance could be determined.

Two experimental plans were used. In plan 1, hearts were perfused antegrade for 1 hr in order to determine steady-state performance. One group of CH and SH were allowed to beat at their own intrinsic rate. In another group tachycardia was created by pacing the atrium at a constant rate. In steady-state experiments cardiac glycogen levels were measured at the end of the experiment. In plan 2, antegrade perfusion was begun with the atrial pressure at 10 cm, and after a control period of 10 min of perfusion the atrial pressure was changed so that a ventricular function curve could be described. In one-half of these experiments the atrial pressure was lowered to 5 cm and then raised in stepwise fashion to 10, 15, and 20 cm (up curve). In the other half of these experiments after the control period, the ventricular function curve was begun at 20 cm and lowered in stepwise fashion to 5 cm (down curve). Hearts were perfused for 7.5 min at each level of atrial pressure. At each level of atrial pressure during the ventricular function curve the aortic tubing was clamped just above the aortic cannula in order to determine cardiac reserve during contraction against a "closed valve." In this situation contraction should be isovolumic. When the heart had reached a stable aortic pressure, the clamp was released. After the ventricular function curve was completed the atrial pressure was returned to 10 cm. In plan 2 all hearts were paced.

Analysis of the experiment. At the end of the experiment hearts were removed, blotted dry, and weighed. The whole heart, or a portion of the ventricles, was then taken for determining the dry weight. Hearts in which glycogen levels were determined were immediately placed in cold perfusion medium at 3°C and blotted; and a portion was placed into preweighed tubes containing 2 ml of 30% KOH. Glycogen was prepared by the method of Walaas and Walaas (13), and the glucose was quantitated enzymatically (14). For lactate, pyruvate, and glucose determinations, 5 ml of perfusate was delivered into tubes containing 1 ml of cold 6% perchloric acid, and the substances were determined enzymatically (15, 16). For calculations of oxygen consumption, oxygen tensions were converted to oxygen content by using the appropriate Bunsen coefficient (17). Oxygen consumption was calculated from the product of the influent minus the effluent oxygen content and the coronary flow expressed per gram dry heart weight per minute.

Cardiac work was calculated from the formula:

$$\text{pressure work (kg-m/min per g)} = \frac{\text{total cardiac output (ml/min)} \times \text{mean systolic pressure (mm Hg)}}{\text{dry weight of heart (g)}} \times 1.36 \times 10^{-5}$$

The mean aortic pressure was calculated from the average of the planimetrically determined area under the ejection phase of three left ventricular pressure curves. The ejection phase was assumed to be that portion of the curve above 62.5 mm Hg (85 cm of water—the pressure of the aortic column). Cardiac output is the sum of aortic flow plus coronary flow.

Cardiac efficiency was calculated from the formula (10):

$$\text{external efficiency (\%)} = \frac{\text{energy output (kcal/min per g)}}{\text{energy input (kcal/min per g)}} \times 100$$

where energy output (kcal/min per g)
= external work (kg-m/min per g)/426.5 (kg-m/kcal)

and energy input (kcal/min per g)
= qO_2 (ml/min per g) × 5.05 (cal/ml O_2) × 10^{-3}.

Mean left ventricular systolic pressure was obtained by planimetry and is the average of three developed pressure curves at each point.

Statistical significance was determined by analysis of variance, and when paired data were compared interaction was employed (18). Regression equations and correlation coefficients were determined by standard formulas (18). Slopes of regression lines were compared as described by Brownlee (19).

RESULTS

Table I shows the effect of the conditioning program upon body weight, heart weight, and heart/body weight ratios. Dry weights are used because perfused hearts gain tissue water (20). This is evidenced in the current experiments by the dry to wet weight ratios which are lower in each group than the ratio of 23.6 ±0.2 (n = 5) found in our laboratory for hearts prior to perfusion. No differences were found between perfused CH and SH in regard to the dry to wet heart weight ratios. The body weights of conditioned rats were significantly lower than controls, and the heart weights were the same in the two groups. The heart weight to body weight ratios were significantly greater in CH. Similar weight relationships have been noted previously in rats conditioned by swimming or treadmill exercise (7, 8, 21).

Steady-state performance. Fig. 1 shows the perfusions with constant filling pressure for 1 hr. As in other perfused rat heart experiments, there was some variability in performance during the first 20 min of perfusion. In the absence of pacing, heart rate and coronary flow were the same in CH and SH. Cardiac output was higher in CH than in SH. Peak left ventricular systolic pressure (PLVSP) showed no differences between CH and SH, but when the product of PLVSP and cardiac output was calculated, this rough correlate of cardiac work was found to be greater in CH than SH. Maximum LV dp/dt and myocardial oxygen consumption (qO_2) tended to be higher in CH than SH. Any differences observed between CH and SH were accentuated by pacing. Furthermore, PLVSP which was not significantly different in the unpaced groups was greater in CH than in SH when the hearts were paced.

When values obtained during pacing are statistically compared with those without pacing at 45 and 60 min, the mean values obtained in paced hearts for cardiac output, coronary flow, PLVSP, or maximum LV dp/dt were not significantly greater than those obtained for

TABLE I

Body Weight and Heart Weight Relationships in Sedentary and Conditioned Rats

	Number of studies		Body weight		Heart weight		Dry heart weight ×100/ wet heart weight		Dry heart weight/ body weight	
	SR	CR	SR	CR	SH	CH	SH	CH	SR	CR
			g		*mg*		%		*mg/g*	
Preperfusion*	6	6	426 ±9	360 ±9‡	230 ±6	245 ±4§	22.0 ±0.5	22.0 ±0.2‖	0.539 ±0.011	0.681 ±0.011¶
Steady state (NP)	15	13	423 ±7	373 ±13¶	242 ±6	242 ±6‖	21.2 ±0.2	21.3 ±0.4‖	0.575 ±0.016	0.656 ±0.026**
Steady state (P)	8	6	438 ±14	370 ±15**	241 ±10	243 ±7‖	20.8 ±0.3	21.5 ±0.5‖	0.544 ±0.015	0.657 ±0.011¶
Ventricular function	8	8	449 ±19	398 ±11**	243 ±9	250 ±8‖	20.6 ±0.4	20.3 ±0.4‖	0.543 ±0.007	0.630 ±0.026**

Results are mean ±SE.
NP, nonpacing; P, pacing; SR, sedentary rats; CR, conditioned rats; SH, hearts from sedentary rats; CH, hearts from conditioned rats.
* Preperfusion indicates after 5 min of retrograde perfusion during which catheters and cannulas were placed.
‡ $P < 0.01$.
§ $P < 0.10$.
‖ $P > 0.1$.
¶ $P < 0.001$.
** $P < 0.05$.

nonpaced hearts at the same time in the experiment. Fig. 2 shows that at 45 and 60 min external work was significantly higher in CH than SH, and the difference was accentuated by pacing. Myocardial qO_2 was higher with pacing than without pacing in CH at both 45 and 60 min. External efficiency usually was the same in CH and SH and did not change with pacing. Fig. 3 shows the differences in myocardial qO_2 and in lactate and pyruvate accumulation at 30 and 60 min with and without pacing. Lactate and pyruvate accumulation was significantly higher in SH with pacing than without pacing. Pacing did not change these metabolites in CH.

Table II shows the carbohydrate data for steady-state experiments. Although cardiac glycogen is usually elevated in hearts of conditioned rats (5–7), no significant differences were observed between CH and SH after 5 min of retrograde preperfusion. At the end of the experiment residual glycogen was also the same in CH

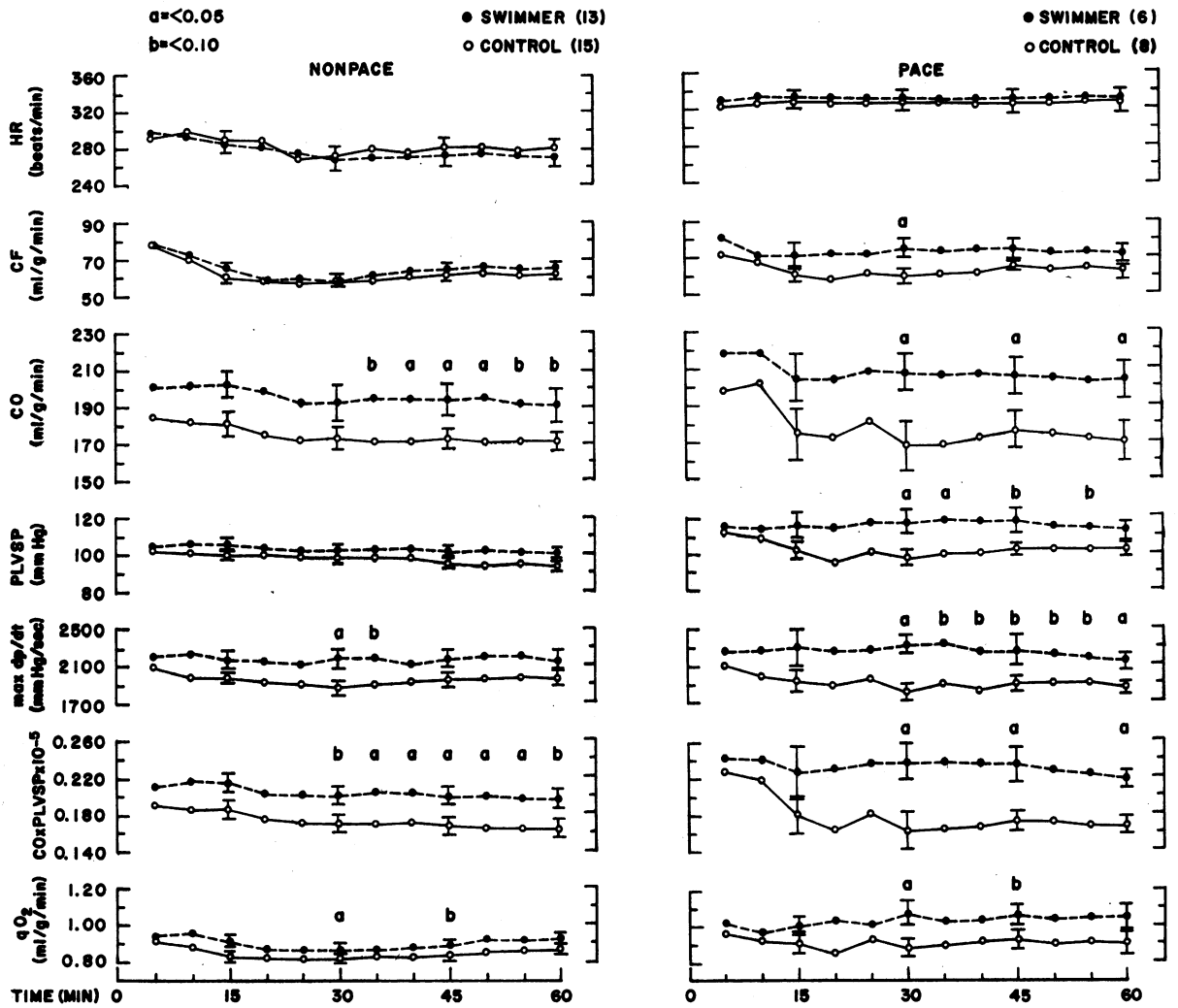

FIGURE 1 Dynamic performance of perfused hearts from conditioned rats (swimmers) and from control rats. Nonpace hearts were allowed to beat at their own intrinsic rate. Pace hearts were paced at constant rates that consistently effected atrial capture. The numbers of hearts are shown in the parentheses. Each point is the mean value for that time. Vertical lines indicate ±SE. Letters above points indicate the level of statistical significance between swimmers and controls at that time. Where no letters are shown $P > 0.1$, except in the CO and CO × PLVSP curves for paced hearts. In both of these curves all points were significantly different ($P < 0.05$) after 30 min. HR, heart rate; CF, coronary flow; CO, cardiac output; PLVSP, peak left ventricular systolic pressure; max dp/dt, the maximum rate of rise of left ventricular pressure; qO_2, oxygen consumption. Values are expressed per gram dry weight.

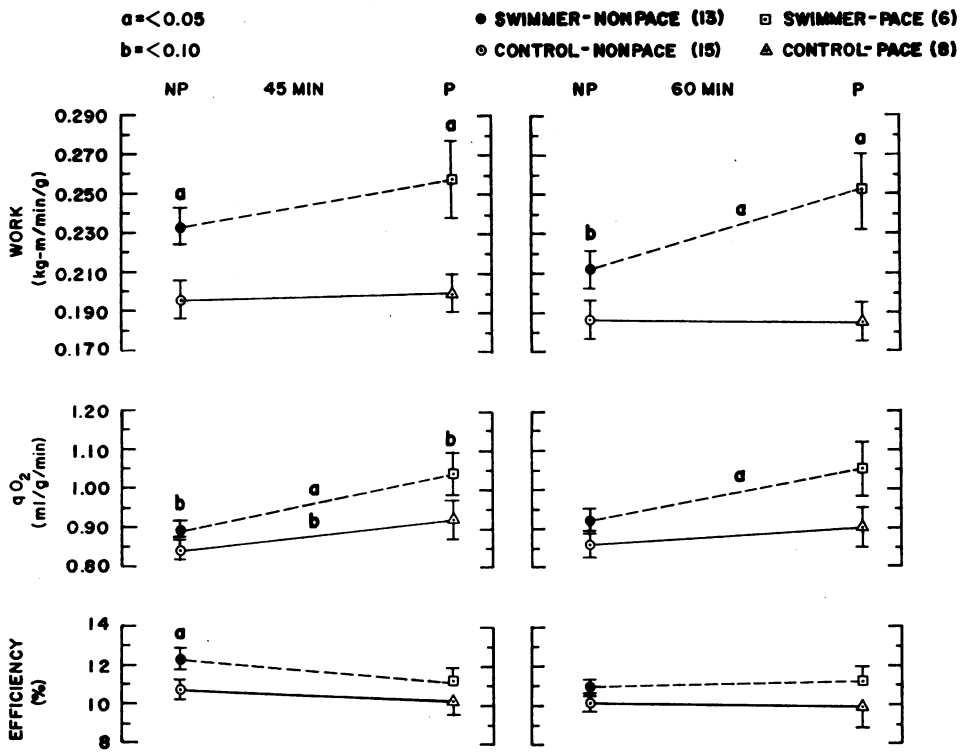

FIGURE 2 Work, oxygen consumption, and efficiency of perfused hearts from conditioned rats (swimmers) and controls at 45 and 60 min. NP, nonpaced; P, paced. The letters along the lines indicate the level of statistical significance when comparing mean nonpace and paced values at a given time. Other designations are the same as in Fig. 1.

and SH, so that about 75% of the glycogen had been metabolized during the experiment in both groups. Glucose utilization did not differ between CH and SH.

Performance with changing atrial pressure. Fig. 4 shows the dynamic results of experiments in which the left atrial pressure was changed. In these experiments all hearts were paced at constant rates of 317 ±3 and 319 ±3 beats per min for SH and CH, respectively. Coronary flow increased in CH, but not in SH, with rising atrial pressure. Cardiac output rose more in CH than SH. Similar directional responses were seen in PLVSP and in maximum LV dp/dt. During the isovolumic clamping periods CH achieved higher systolic pressures and maximum LV dp/dt than SH. Whereas the performance levels achieved while the aortic tubing was clamped were similar at 10, 15, and 20 cm of atrial pressure in CH, the means for PLVSP and maximum LV dp/dt were less during isovolumic performance at 20 cm atrial pressure than at 10 cm in SH ($P < 0.05$ and $P < 0.1$, respectively).

The curves in Fig. 4 are pooled up and down experiments. When up curves are separated from down curves some differences are observed. No matter in which direction the curves were performed CH appeared to to perform better than SH. However, when an atrial pressure of 20 cm initiated the curve, SH showed lesser performance during the remainder of the curve than if the curve had been initiated with 5 cm perfusion. It appeared that SH could not withstand the stress of increased atrial pressure as well as CH.

Fig. 5 shows the relationship of left ventricular work, mean LV systolic pressure, oxygen consumption, lactate production, and efficiency to change in atrial pressure. As shown by these measurements CH had improved mechanical function when compared with SH. Myocardial oxygen consumption appeared to parallel changes in work and in mean left ventricular systolic pressure, both in CH and in SH. CH achieved a higher mean oxygen consumption than SH. To compare the relation of qO_2 to mechanical function, regression lines were calculated with qO_2 as the dependent variable and work, mean systolic pressure, and cardiac output as separate independent variables for CH and for SH. Significant correlation coefficients ($r > 0.7$, $P < 0.05$) were found for all relationships, but there were no significant differences in the slopes of the regression lines between SH and CH. As in steady-state experiments, lactate production tended to be higher in SH than in CH.

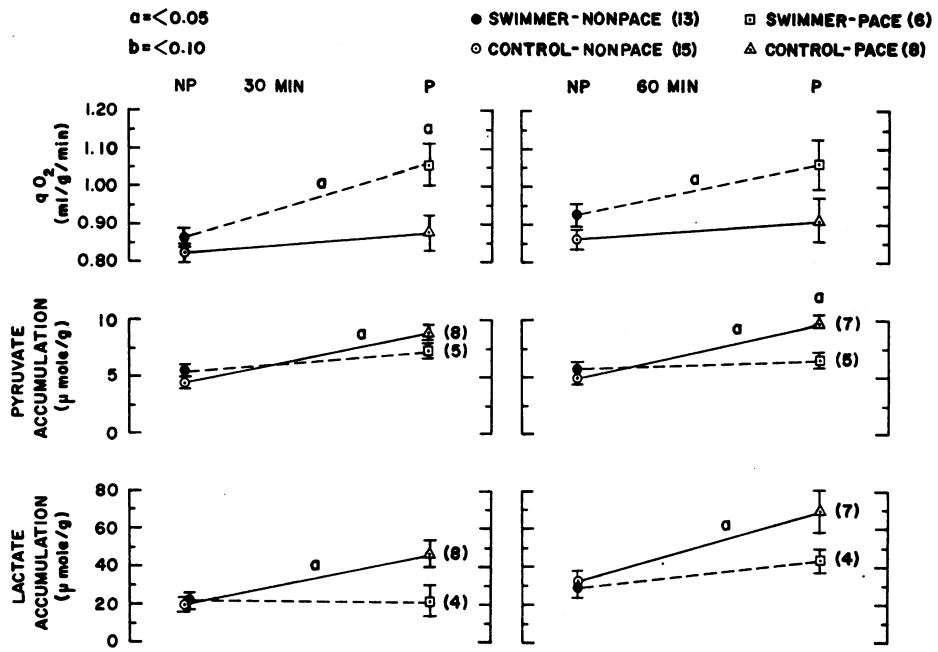

FIGURE 3 Oxygen consumption and lactate and pyruvate accumulation of perfused hearts at 30 and 60 min. Symbols and designations are the same as in Fig. 2.

When aerobic ATP production and anaerobic production were estimated, the mean ratio between the two was always higher in CH than SH. At an atrial pressure of 5 cm these ratios were 25:1 in CH and 9:1 in SH. At 20 cm the ratios were 6:1 and 4:1, respectively. At 10 and 15 cm the ratios were intermediate.

The mechanism of the increased oxygen consumption differed in CH and SH. In CH it was mainly due to a 20% increase in coronary flow ($P < 0.05$), and the extraction of oxygen from the perfusing fluid did not change significantly (13.9–14.2 μl/ml, $P > 0.2$). In SH the coronary flow did not change significantly, but extraction rose 15% from 13.0 to 14.9 μl/ml ($P < 0.01$).

When performance during the initial control period, the atrial pressure being 10 cm, is compared with the performance when the perfusion pressure was returned to 10 cm after completion of the ventricular function curve, it appears that SH had deteriorated faster than CH. In SH coronary flow, cardiac output, oxygen consumption, and left ventricular work were significantly

TABLE II
Carbohydrate Metabolism in Perfusion Experiments

	Number of hearts	Initial glycogen*	Glucose uptake		Lactate accumulation		Pyruvate accumulation		Residual glycogen	Lactate/pyruvate	
			30 min	60 min	30 min	60 min	30 min	60 min	60 min	30 min	60 min
		μmoles/g	*μmoles/g*		*μmoles/g*		*μmoles/g*		*μmoles/g*		
Nonpacing											
Control	15	27.9 ±2.3	38.7 ±10.2	65.8 ±8.3	20.5 ±3.8	31.6 ±4.8	4.5 ±0.4	4.5 ±0.5	6.0 ±0.5	4.6	7.0
Swimmer	13	29.1 ±1.7‡	45.8 ±10.0§	62.2 ±9.2‡	20.8 ±4.4‡	42.2 ±6.9‡	5.4 ±0.6§	5.1 ±0.8‡	6.8 ±0.7‡	3.9	8.3
Pacing											
Control	8	27.9 ±2.3	43.4 ±4.3	76.9 ±17.1	47.5 ±6.8	66.0 ±12.0	8.8 ±0.6	9.4 ±0.6	7.2‖	5.4	7.0
Swimmer	6	29.1 ±1.7‡	44.0 ±8.9‡	70.4 ±24.3‡	28.6 ±5.6‡	40.7 ±6.1‡	7.2 ±0.8‡	6.8 ±0.8¶	6.8‖	4.0	6.0

Results are per gram wet weight, mean ±SE.
* Mean of six hearts from conditioned and sedentary rats perfused retrograde for 5 min.
‡ $P > 0.1$.
§ $P < 0.1$.
‖ Two hearts only.
¶ $P < 0.05$.

lower ($P < 0.05$) during the final period than in the initial period. Peak systolic pressure, maximum LV dp/dt, and mean systolic pressure showed no differences between these two times. In CH coronary flow was the only variable that showed a significant decline between the initial and final periods.

DISCUSSION

The design of the current experiments does not permit complete analysis of the fundamental mechanochemical relationships in these hearts. In order to accomplish this accurate determination of tension, contractility and extent of fiber shortening should be available (22, 23). Ventricular volumes were not determined, and therefore, these variables cannot be accurately quantitated. However, it has been reported that passive length-tension curves of myocardium from rats that had been chronically swum are normal (4, 24). This suggests that at the same atrial pressure the diastolic volume of CH and SH would be the same. Since tension is the most costly determinant of energy use, and oxygen consumption was higher in CH than SH, it is probable that tension development was also greater in CH. If the left ventricular volume was the same in the two groups of hearts, tension development would be proportionate to the mean ventricular systolic pressure. Mean LV systolic pressure tended to be greater in CH than in SH and paralleled the differences observed for oxygen consumption.

Since cardiac output was higher in CH than SH, but heart rates were comparable in the two groups, stroke volume was greater in CH. If diastolic volumes were the same or smaller in CH than SH, this implies that the extent of fiber shortening during contraction must also have been greater in CH (25). When atrial pressure was increased the occompanying rises in cardiac output and cardiac work in both CH and SH were proportionately greater than changes in myocardial oxygen consumption, and calculated efficiency increased significantly. This confirms the fundamental observation that fiber shortening is less costly in terms of energy consumption than is tension (23).

The increase in maximum rate of pressure development with elevations in ventricular filling pressures appears to be independent of contractility (26). However the differences between CH and SH in maximum LV dp/dt at comparable heart rates, preloads, and afterloads might indicate increased contractility in CH. This is

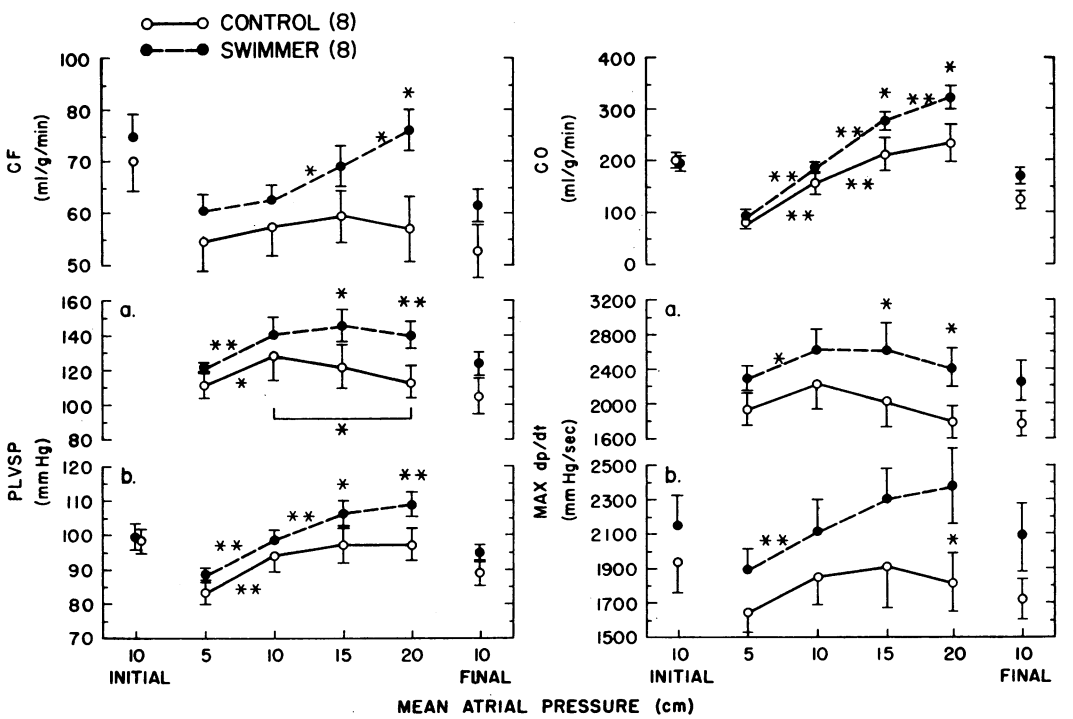

FIGURE 4 The effect of changing atrial pressure on dynamic performance of hearts from conditioned rats (swimmers) and control animals. *a* indicates values obtained when the aortic tubing was clamped. *b* indicates values with the aortic pressure 85 cm of fluid. Asterisks along the lines indicate that paired mean points among swimmers or controls are significantly different. Asterisks above the points indicate that at that atrial pressure the difference between swimmers and controls is significant. *, $P < 0.05$; **, $P < 0.01$.

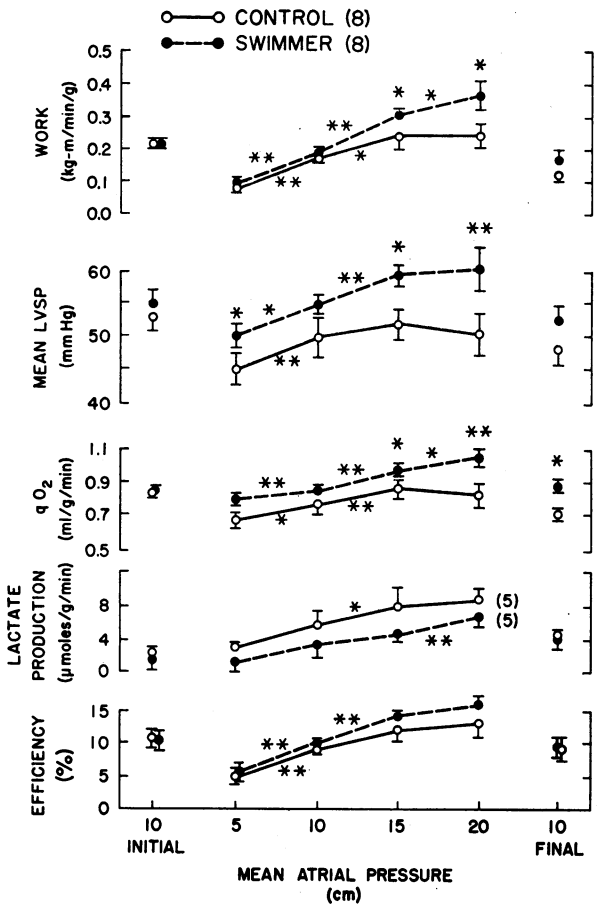

FIGURE 5 The effect of changing atrial pressure upon work, mean left ventricular systolic pressure, oxygen consumption, lactate production, and efficiency. Designations are the same as in Fig. 4.

only true if ventricular volumes were the same or were larger in CH.

It appears that all three determinants of myocardial energy use (tension, fiber shortening, and contractility) are probably the same or are greater in CH than SH, especially during stress.

This type of energetic analysis is not informative in regard to the pumping characteristics of the heart. Cardiac output and cardiac work are important in this regard and might correlate better with the potential in the intact animal for delivering oxygen to the peripheral tissues. Examination of these variables separates CH and SH, especially in their response to pacing or increasing atrial pressure, and indicates that CH have greater reserve capacity than SH.

The concept that CH have increased reserve is supported by several other observations. When ventricular function curves were performed in the down direction the early perfusion with 20 cm filling pressure resulted in more rapid deterioration in performance in SH than in CH. Up curves showed lesser differences in performance. Comparison of initial and final performance with 10 cm perfusion, before and after ventricular function experiments, shows significant deterioration only in SH. The isovolumic clamping studies also show deteriorating function at atrial pressures of 15 and 20 cm only in SH but not in CH.

There are several possible reasons for the increased reserve in CH. The possibility of a smaller ventricular volume and increased efficiency of converting chemical energy to pressure must be considered (25). However, higher oxygen consumption was achieved in CH than SH, indicating that this could not be the sole factor. The increased oxygen use might result from greater mechanical demand for energy use in CH or a greater capacity to metabolize oxygen. The finding that lactate production tended to be higher in SH supports the concept that the aerobic capacity of CH was greater than of SH. A greater aerobic potential might be the result of biochemical adaptation of tissue from conditioned animals. Skeletal muscle from conditioned rats has increased aerobic enzyme activities and elevated cytochrome c levels, and these are associated with enhanced mitochondrial oxidative capacity (27). Similar changes might occur in myocardium. Oxygen delivery may have been a limiting factor in SH, accounting for the lower performance in those hearts.

In physiologic states oxygen delivery to the myocardium is proportional to flow, and the arteriovenous oxygen difference remains quite constant (28). When oxygen needs are diminished, coronary flow declines, and the arteriovenous oxygen difference is constant or narrows slightly. However, when coronary flow becomes a limiting factor in oxygen delivery, the arteriovenous oxygen difference increases (29). Thus, under physiological conditions an increased arteriovenous oxygen difference implies a limitation in the ability of the coronary vessels to deliver blood. In the present experiments, oxygen extraction increased significantly during stress only in SH, and conversely, coronary flow increased significantly in CH but not in SH. The present data suggest that the coronary vasculature was a limiting factor in the response to stress in SH. These findings are consistent with the observation in chronically exercised rats that the coronary vasculature increases (21, 30).

When studying perforance of isolated hearts it is important to compare hearts of similar size (10). Cardiac work per gram of myocardium is less in large hearts than in small hearts. Heart rate should also be the same so that the inotropic effect of rate is eliminated (26). In the current experiments the heart rates and heart weights were similar in both groups of animals.

We did not measure heart rate or blood pressure in vivo in our conditioned rats. Relative bradycardia is usually present in conditioned rats (3, 31) and other conditioned animals, and blood pressure is reported to be unchanged (3). Intrinsic heart rate in perfused CH and SH was the same in the current experiments. This might be analogous to the finding with catecholamine-depleted hearts, which exhibit bradycardia in vivo, but beat at the same rate as control hearts when perfused in the isolated state (32).

The similarity of heart weight between CH and SH raises the question of adequacy of conditioning in these animals. Previous studies have shown that when rats are subjected to moderate treadmill exercise or swimming, heart weight is not uniformly increased (7, 21). Even with more severe exercise, differences in heart weight are only borderline (3). The training regimen used in the current experiments has previously been shown to be associated with consistent changes in myocardial glycogen stores (7), indicating that some adaptation had occurred. The finding that ventricular function is improved supports the assumption that significant conditioning had occurred in these rats. It is possible that more strenuous exercise would have resulted in more marked differences in performance.

Previous experiments conducted in the open chest rat using a strain gauge arch (3) and studies in which the mechanics of isolated trabeculae carneae were investigated (4) indicated that tension development could be greater in hearts of conditioned rats than in hearts of sedentary animals. In the studies of Adlinger and Crews (3) heart rates and cardiac mass differed in control and conditioned animals. The present studies investigated cardiac performance in the whole heart under conditions in which heart weight and rate, preload, and afterload were similar in experiments with CH and SH. The function of the heart as a pump could be studied under a variety of conditions. Our results extend the earlier observations and indicate that hearts of conditioned animals can respond to stress not only with greater tension development, but with greater external cardiac work. This increased mechanical response appears to be related to a greater capacity for adjustment in coronary flow in hearts from conditioned rats. Therefore, in addition to the heart rate and stroke volume adaptations seen with conditioning in the intact animal, in the rat intrinsic cardiac alterations contribute to the improved cardiac performance in physical training.

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